UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/720,323	11/24/2003	Jill Giles-Komar	CEN 249CIPNP	6412

27777 7590 02/27/2006

PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/720,323	GILES-KOMAR ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *28-51,54 and 59-66* is/are withdrawn from consideration.

5)☒ Claim(s) *11* is/are allowed.

6)☒ Claim(s) *1-10,12-27,52,53 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/23/4, 7/12/4 &2/* ~~1465~~ 1-14-05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-66 are pending.

2. Applicant's election without traverse of Group I, claims 1-27, 52-53 and 55-58 drawn to an isolated monoclonal antibody which binds to human alpha V integrin subunit, immunoconjugates, pharmaceutical compositions thereof, and an article of manufacture and the species of SEQ ID NO: 8 and 8 filed on 11/25/05, is acknowledged.

3. Claims 28-51, 54 and 59-66 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Applicant's IDS, filed 4/23/4, 7/12/04 and 2/14/05, is acknowledged, however, Maxime Lehmann et al reference listed in the IDS filed 4/23/04 is crossed out because it is duplicate of Lehmann et al reference listed on the same IDS. Further, only English abstract of reference AO listed on the IDS filed 7/12/04 is considered.

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Page 31 line 30 through page 32, line 18 contains embedded hyperlinks and/or other forms of browser-executable code which are impermissible and require deletion.

6. Claims 5-6, 12-27, 52-53 and 56-58 are objected to under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim.

7. Claim 55 is objected to because it is dependent on a non-elected claim 54 and should be written as an independent claim.

8. Claim 8, line 3 is objected to because in listing species of the heavy chain variable region the conjunction "or" should be use rather than "and".

9. Claims 7, 8 and 21 are objected to for the following informalities:
   (a) "SEQ ID NOs: 8" in claim 7, line 6 is misspelled, the correct spelling is "SEQ ID NO: 8",
   (b) the word "Of" in claim 8 should be "of",
   (c) the double ", ," recited in claim 21, line 9 should be one ",".

10. The term "KD/K_D" has been referred to as "KD" in claims 4 and 9 or "K_D" in claims 7 and 7. Consistency is required.

11. The parenthesis "()" in claim 9 is objected to because it is unclear whether the recited elements between the parenthesis are essential elements of the claim or not.

12. Claims 21 and 22 are objected to because the Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" rather than "or" in listing the species. In the instant claim 21 it is unclear whether "selected from at least one of a detectable label or reporter, an anti-neoplastic agent .... or a cytokine antagonist" is a Markush species listing or not. Similarly, in claim 22, it is unclear whether "selected from a radiopharmaceutical ... and a radiosensitizer" a Markush species listing or not.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 4-6, 9, 12-27, 52-53 and 56-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 4-5 are indefinite in the recitation of "CNTO 95" because its characteristics are not known. The use of " CNTO 95" germline sequence as the sole means of identifying the claimed germline sequence renders the claim indefinite because " CNTO 95" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct hybridomas or cell lines germline. It is suggested that the SEQ ID NO: 7/8 be cited in the claims.

B. Claim 9 is indefinite because it lacks the conjunction "and" in lasting the species (a), (b) and (c).

C. The recitation "at least one activity of at least one alpha-V subunit protein" in claims 14 and 58 is indefinite because it is unclear what activity is contemplated.

D. Claim 18 is indefinite because claim 18 which depends from any of preceding claims including claim 13, recites a human antibody, while independent claim 13 is already a human antibody.

E. The "dacarbazine" recited in claims 23 has no antecedent basis in base claim 22. Base claim 22 only recites a radiopharmaceutical, an estrogen receptor modulator, a retinoid, a topoisomerase inhibitor, a cytotoxin, an alkylating agent, a nitrogen mustard, a nitrosourea, an antimetabolite, a mitotic inhibitor and radiosensitizer.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 5-6, 12-27, 52-53 and 56-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Since the isolated monoclonal antibody requires both VL and VH each comprising FR1, FR2, FR3 and FR4 and the specification does not provide CNTO 95 germline sequence in claims 5-6. Further, It is apparent that the M21 cell claimed in claim 15 is required to practice the claimed invention. Therefore, the recombinant cells that produce the CNTO 95 germline sequence and the M21 cell are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the germline and the M21 cell, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposits have been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the germline sequence and M21 cell has been deposited under the Budapest Treaty and that the germline sequence and M21 cell will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of the patent whichever is longer*. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposits were made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the germline sequence and cell described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Further, amendment of the specification to disclose the date of deposit and the complete name and address of the depository (ATCC.10801 University Boulevard, Manassas, VA 20110-2209) is required as set forth in 37 C.F.R. 1.809(d).

17. Claims 1-10, 12-27, 52-53 and 55-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated human monoclonal antibody comprising a heavy chain variable region comprising FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4 sequences and the light chain variable region comprising FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4 sequences, wherein heavy chain variable region of CDR1 is SEQ ID NO: 1, CDR2 is SEQ ID NO: 2 and CDR3 is SEQ ID NO: 3, the light chain variable region of CDR1 is SEQ ID NO: 4, CDR2 is SEQ ID NO: 5 and CDR3 is SEQ ID NO: 6 or an isolated human monoclonal antibody comprising the heavy chain variable region comprising the amino acid sequence of SEQ ID NO:7 and the light chain variable region comprising the amino acid sequence of SEQ ID NO: 8, a composition thereof, an immunoconjugate thereof, an article of manufacture thereof, does not reasonably provide enablement for any isolated monoclonal antibody comprising a heavy chain variable region comprising FR1, CDR1, FR2, CDR2, FR3, CDR3, and F4 sequences and a light chain variable region comprising FR1, CDR1, FR2, CDR2, FR3, CDR3, and F4 sequences and "conservative modifications thereof", (b) the light chain variable region CDR3 sequence is selected from SEQ ID NO: 6, and " conservative modifications thereof" in claim 1, wherein the heavy chain variable region CDR2 sequence is selected from SEQ ID NO: 2, and "conservative modification thereof" and the light chain variable region CDR2 sequence is selected from SEQ ID NO: 5 and "conservative modifications thereof" in claim 2, wherein the heavy chain variable region CDR1 sequence is selected from SEQ ID NO: 1, and "conservative modification thereof" and the light cahin variable region CDR2 sequence is selected from SEQ ID NO: 4 and "conservative modifications thereof" in claim 3, which binds to human alpha V integrin subunit with a KD of 10^{-8} M or "less" in claim 4, wherein the heavy chain variable region FR1, FR2, FR3 and FR4 sequences are derived from the heavy chain "CNTO 95 germline sequence" in claim 5, wherein the heavy chain variable region FR1, FR2, FR3 and FR4 sequences are derived from the heavy chain "CNTO 95 germline sequence" in claim 6, or an isolated monoclonal antibody comprisig a heavy chain variable region and a light chain variable region, wherein : (a) the heavy chain variable region comprises an amino acid sequence consisting of SEQ ID NO: 7, or "sequences that are at least 80% homologous to SEQ ID NO:7"; (b) the light chain variable region comprises any amino acid sequence selected from the group consisting of SEQ ID NO: 8, and "sequences that are at least 80% homologous to SEQ ID NO: 8 and (c) the antibody binds to human alpha v integrin subunit with a K_D of 10^{-8} M or "less" in claim 7, wherein the antibody binds to human apha V integrin subunit with a K_D of 10^{-9} or "less" or an isolated monoclonal antibody comprising a heavy chain variable region "derived from" the heavy chain CNTO 95 germline sequence (SEQ ID NO: 7), and a light chain variable region "derived from" the light chain CNTO 95 (SEQ ID NO: 8) germline sequence, wherein : (a) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 7 or a "sequence that is at least 80% homologous to SEQ ID NO: 7, (b) the light chain variable region comprises the amino acid sequence of SEQ ID NO: 8 or " a

sequence that is at least 80% homologous to SEQ ID NO: 8" and ; (c) the antibody binds to human alpha V integrin subunit with a KD of 10-8 M or "less" in claim 9, or an isolated anti-alpha-V subunit monoclonal antibody comprising "at least one variable region" comprising SEQ ID NO: 7 or 8 in claim 10 or an isolated monoclonal antibody that "competes for binding" to human alpha V integrin subunit with the mono claonal antibody of any one of the preceding claims in claim 12, or an isolated human antibody of any one of the preceding claims produced by hybridoma, wherein the hybridoma is prepared from a B cell obtained from a transgenic non-human animal having a genome comprising a human heavy chain transgene or transchromosome and a human light transgene or transchromosome, fused to an immortalized cell in claim 13, or an alpha- subunit antibody wherin said antibody substantially neutralizes at least one activity of at least one alpha-subunit protein in claim 14, the antibody of any one of the preceding calims which completely inhibits M21 cell adhesion to vitronectin in claim 15, the antibody of any one of the preceding claims, comprising a human IgG heavy cahin and a human Kappa light chain in claim 16, the antibody of any one of the preceding claims, comprising an IgG1 or IgG3 heavy cahin in claim 17, the antibody of any one of the preceding claims, which is a human antibody in claim 18 or a pharmaceutical composition comprising the antibody of any one of the preceding claims and a pharmaceutically acceptable carrier in claim 19, or a composition comprising at least one isolated mammalian anti-alpha-V subunit antibody having at least one variable region comprising SEQ ID NO: 7 or 8, and at least one pharmaceutically acceptable carrier or diluent in claim 20, or a composition to claim 19 or claim 20 further comprising at least one composition comprising an effective amount of at lest one compound or protein selected from the group listed in claim 21, or a composition according to claim 19, wherin the antibody is combined with antineoplastic agent selected from the group listed in claim 22, wherein the anti-neoplastic agent is dacarbazine in claim 23 or an immunoconjugate comprsing the antibody according to any one of the preceding claims linked to any therapeutic agent in claim 24, wherein the therapeutic agent is a cytotoxin in claim 25, wherein the therapeutic agent is a radioisotope in claim 26, a pharmaceutical composition comprising the immunoconjugate of any one of claims 24-26 and a pharmaceutically acceptable carrier in claim 27 or an article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising a solution or a lyophilized form of at least one isolated human anti-alpha-V subunit antibody according to any one of claims 1-18, wherein said container is a component as recited in claim 53, at least one anti-alpha-V subunit antibody produced by a method according to claim 54, at least one isolated mammalian anti-alpha-V subunit antibody that binds to "the same epitope" of an alpha-V subunit portien as an antibody according to any one of claims 1-18 in claim 56, wherein said antibody binds apha-V subunit with an affinity of at least one selected from at least 10^{-9} M, at least 10^{-10} M, at least 10^{-11} M or at least 10^{-12} M in claim 57, wherein said antibody substantially neutralizes at least one activity of at least one alpha-V subunit portein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to make and use monoclonal antibodies comprising the VH and VL each comprising either the CDR1, CDR2 or CDR3 respectively or "conservative modification thereof". Claims 7 and 9 recite "sequences are at least 80% homologous to SEQ ID NO: 7/8". However, it is well established in the art that the formation of

an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that monoclonal antibody as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an CNTO 95, human monclaonal antibody, in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce imunoconjugate proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional monoclonal antibody can be obtained by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody. As evidenced by Adair et al. (US Patent 6,632,927) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (col.2 lines 58-61). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity.

Similarly, the 20030143603 teaches anti-tumor necrosis factor antibody light chain variable region comprising the claimed SEQ ID NO: 8 (see published SEQ ID NO: 8), providing evidence that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a CNTO 95 antibody. Therefor, an antibody that comprising at least one variable region comprising SEQ ID NO: 7 or 8 would not result in an anti-alpha-V binding antibody.

In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

Claims 5-6 fail to establish the structure of "CNTO 95" germline sequence to which the claimed human monoclonal antibody derived. "CNTO 95" is arbitrary germline names. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of "CNTO 95" germline sequence broadly encompassed by the claims.

Further, at issue claim 13, the claim is not enabled because the skilled artisan would not know what antigen to immunized in order to produce the claimed antibody.

Also, at issue claims 12 and 56-58, because the specification fails to teach the specific epitope which the claimed CNTO 95 binds. It would require undue experimentation from the skilled artisan to determine the epitope of the claimed antibody and then produced human monoclonal antibodies that would compete for binding to alpha-V subunit of integrin of the claimed CNTO 95. The specification fails to teach any human antibody that competes with the claimed CNTO 95.

In addition, claim 20 recites mammalian anti-alpha-V subunit antibody having at least one variable region comprising SEQ ID NO:7 or 8. It is noted that both VH and VL of SEQ ID NO: 7 and 8 respectively are derived from human CNTO 95 germline sequence. Since CNTO 95 antibody binds to human alpha V integrin subunit but not bind mouse alphaV integrin (see page 125, line 15-16). A mammalian immunoglobulin comprising either SEQ ID NO: 7 or 8 would be result in would have the same binding property as the original CNTO 95 and is likely to be more immunogenic in humans. There is no use of such antibodies in human.

It is noted that claim 21 recites that the claimed composition further comprises any immunization any immunoglobulin, hormone release modulator, any epinephrine analog among others without disclosed beneficial for such protein or analogs in the specification.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claim 12 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Wayner et al (1991) as is evidenced by CHEMICON INTERNATIONAL catalog number MAB1953Z.

Wayner et al teach monoclonal antibodies, P3G8 and LM142, directed to the human αv integrin subunit (see page 920, 1st col., under Antibodies and 2nd col., under Results in particular). While the reference is silence with respect to an IgG1 heavy chain, CHEMICON INTERNATIONAL catalog number MAB1953Z teaches that the P3G8 antibody is IgG1 isotype (see page 1, in particular).

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not compete with the recited antibodies in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

20. Claim 12, 14-17, 19, 21, 24, 27 and 55-58 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S Pat. No. 5,985,278 (IDS Ref. No. A2).

The US `278 patent teaches several monoclonal antibodies such as 17E6, 20A9, 23G5 and 14E2 (all are IgG1/k isotype) which reacting only with the αv chain of human αv integrin, blocking the attachment to the integrin substrate such as vitronectin of the αv integrin bearing cell such as M21 cells (see table 1 in particular), triggering reversal of established cell matrix interaction caused by αv integrins, blocking tumor development and showing no cytotoxic activity (see table 3, abstract and claims 1-23 in particular). The `278 patent further teaches that a pharmaceutical composition comprising the monoclonal antibody and a pharmaceutically acceptable carrier (see patented claims 4 and 6 in particular). The `278 patent teaches that other additives such as antibiotics (i.e., antimicrobial) may also be present in the pharmaceutical formulations (see col. 19, lines 59-62 in particular). In addition the `278 teaches the antibody can also be conjugated according to known methods to cytokines such as IL-2 in order to support their cytotoxicity (see col., 19, lines 63-65 in particular). Finally, the `278 patent teaches that the results corroborated the ELISA data with purified receptors. MAbs with specificities for β3, and GpIIb were also obtained in the screen (data not shown), and these reacted in a way clearly discrete from the alpha-v group. 17E6, 14D9.F8, 20A9 and 23G5 bound αvβ3 with similar apparent affinity. 50% binding was achieved at ~10-20 ng ml^{-1} (~50-100 pM--similar to LM609), i.e., $5X10^{-11}$M to 10^{-10}M (see col., 6, lines 18-28 in particular).

Claim 55 is included because an antibody is an antibody irrespective of how it is made.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not compete with the recited antibodies in the claim or does not bind to the same epitope of an alpha-V subunit protein recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

21. Claims 12-13 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S Pat. No. 5,985,278 (IDS Ref. No. A2) in view of U.S. Pat. No. 5,877,397.

The teachings of `278 patent, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of human antibody in claims 13 and 18.

The '397 patent teaches that it is desirable to produce human immunoglobulins that are reactive with specific human antigens that are promising therapeutic and/or diagnostic targets. The '397 patent teaches gene segments are derived from human beings. The transgenic non-human animals harboring such heavy and light transgenes are capable of mounting an Ig-mediated immune response to a specific antigen administered to such an animal. B-cells are produced within such an animal which are capable of producing heterologous human antibody. After immortalization, and the selection for an appropriate monoclonal antibody (Mab), e.g. a hybridoma, a source of therapeutic human monoclonal antibody is provided. Such human Mabs have significantly reduced immunogenicity when therapeutically administered to humans (see col. 18, lines 8-19 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by '278 patent as a human antibody as taught by the '397 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because human Mabs have significantly reduced immunogenicity when therapeutically administered to humans taught by the '397 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this

application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 1-23, 27, 52-53 and 55-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 10-11, 17-18, 20-23, 29-30, 37-39, 41-43, 49-50, 57-58, 60-63, 69-70, 77-78, 80-83, 89-90, 97-98 and 100 of copending Application No. 09/920,267. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the copending Application are claiming isolated human and CDR-grafted anti-alpha-V integrin subunit antibodies. The claimed SEQ ID NO: 1-8 are identical therefore the binding specificity of both antibodies are the same. Further the anti-alpha V antibody is suitable for administration by parentaeral, subcutaneous, intramuscular, intravenous, intraraticalar, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary intracelebellar, or other routes. Since the VL and VH are the same in both application, then the FR1-FR4 are the same and the claim function inhibition of M21 cell adhesion to vitronection would be inherent property of the same product. Finally, both applications claim an article of manufacture comprising the antibody and a pharmaceutical composition comprising the claimed antibody which further comprising at least a compound or protein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 24-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 10-11, 17-18, 20-23, 29-30, 37-39, 41-43, 49-50, 57-58, 60-63, 69-70, 77-78, 80-83, 89-90, 97-98 and 100 of copending Application No. 09/920,267 in view of US. Pat. No. 6,342,221.

The teachings of the `267 copending Application has been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of an immunoconjugate comprsing the antibody linked to a therapeutic agent in claim 24, wherein the therapeutic agent is a cytotoxin in claim 25 or a radioisotope in claim 26.

The `221 patent teaches that it will be readily appreciated by those of skill in the art that the immunoconjugate and prodrug forms of the present treatment methods have the distinct advantage of providing a single therapeutic agent with two properties: the inherent anti-angiogenic property of the antibody and the therapeutic property of the attached agent (e.g., cytotoxic, coagulative, apoptopic, etc). The conjugated and prodrug treatment forms of the

present antibodies thus have an incredibly wide utility throughout the field of cancer treatment (see col. 106, lines 34-42 in particular). The `221 patent further teaches that the second anti-cancer therapeutics can be operatively attached to any of the cytotoxic or otherwise anti-cellular agents such as radioisotopes (see col., 125, lines 14-20 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to immunoconjugate the antibody taught by the `267 copending application with either a cytotoxin or a radioisotope as taught by the `221 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the resultant immunoconjugate would have the distinct advantage of providing a single therapeutic agent with two properties: the inherent anti-angiogenic property of the antibody and the therapeutic property of the attached agent as taught by `221patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

This is a provisional obviousness-type double patenting rejection.

25. No claim 11 is allowable.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 27, 2006

Maher Haddad

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600